## REMARKS

**Rejection for double-patenting under the judicially created doctrine of obviousness-type double patenting**

Claims 19-37 have been rejected under the judicially created doctrine of obviousness-type double patenting as being obvious over claims 1, 6, 7 and 9 of U.S. Pat. No. 6,376,745. Attached hereto is a terminal disclaimer, disclaiming any term of any patent issued from the present application that would extend beyond the term of the '745 patent. Withdrawal of the rejection is therefore respectfully requested.

**Rejections under 35 U.S.C. §112, first paragraph**

Claims 26, 36 and 37 have been rejected under 35 U.S.C. §112, first paragraph for lack of enablement with the assertion that the claims are not enabled for other eukarytotic cells than yeast and plants. Applicants traverse this rejection and withdrawal thereof is respectfully requested. The Examiner's attention is directed to Example 7 of the specification, wherein plant viral IRES-mediated GUS gene expression in human (HeLa) cells is disclosed. In addition, attached hereto as Exhibit A is a journal article of Dorokhov et al. PNAS 99:5301-5306 (2002), which further discloses the activity of IRES elements of the invention in HeLa cells. As

such, the enablement of the invention as claimed has been fully supported. Withdrawal of the rejection is therefore respectfully requested.

**Rejections under 35 U.S.C. §112, second paragraph**

Claims 23 and 24 have been rejected under 35 U.S.C. §112, second paragraph as being unclear. More specifically, claims 23 and 24 have been rejected as being unclear in the recitation of "i.e." Claims 23 and 24 have been amended for clarity by replacing "exhibiting IRES activity, i.e. being" with "is." Withdrawal of the rejection is therefore respectfully requested.

**Rejections under 35 U.S.C. §102(b)**

Claims 19, 20, 25, 27, 31, 34, 36 and 37 have been rejected under 35 U.S.C. as being anticipated by Thomas et al. Thomas et al. is asserted to teach a bicistronic vector comprising a full-length clone of cowpea mosaic virus middle component RNA (CPMV M-RNA) with a T7 RNA promoter. The Examiner asserts that the CPMV M-RNA of Thomas et al. has two functional initiation sites, with one at the 5′ end and the other at an internal initiation site, which result in the translation of two protein products. The Examiner asserts that the CPMV M-RNA of Thomas et al. therefore meets the

limitations of the present invention. Applicants traverse this rejection and withdrawal thereof is respectfully requested.

As will be shown with the remarks that following, the CPMV M-RNA of Thomas et al. does not contain an IRES and the activity reported in the paper is an artifact of a poorly controlled experiment.

Thomas et al. introduced the CPMV middle component into the ornithine decarboxylase (ODC) gene. However, the ODC gene itself contains an IRES. See for example the attached Abstract of Pyronnet et al. Mol. Cell 5:607-616 (2000) (Exhibit B1). At the same time Thomas et al. failed to do a negative control for IRES activity from the ODC gene itself. As shown below, the activity observed by Thomas et al. is, in fact, from the native IRES of the ODC gene and not from the inserted CMPV middle component.

It is accepted that to conclusively identify a sequence as being an IRES requires tests on the expression of a 5' distal reporter gene, such as GUS, from a bicistronic construct *in vivo*. See Kozak, Mol. Cell Biol. 21:1899-1907 (2001) (Exhibit B2). The identity of the present IRES was confirmed by the inventors using such experiments and similar experiments were also performed by the authors of Dorokhov et al. (Exhibit A). The authors of Thomas et al. neither used bicistronic constructs nor performed *in vivo*

experiments. Thus, it cannot be scientifically concluded from Thomas et al. that the CPMV middle component contains an IRES.

A further piece of evidence that the CPMV middle component does not contain an IRES is the fact that a search of the database found at http://rangueil.inserm.fr/iresdatabase, which is a comprehensive list of IRES elements does not list CPMV as an IRES.

Finally, attached hereto as Exhibit B3 is an article by Belsham and Lomonossoff, J. Gen. Virol. 72:3109-3113 (1991), wherein the suggestion by Thomas et al. that CPMV contains an IRES has been tested. See pate 3109, right column, lines 12-21. Belsham and Lomonossoff confirm the points of the discussion above and demonstrate that internal initiation of translation is not responsible for the synthesis of the 95 K protein of CPMV M-RNA. Belsham and Lomonosoff state on page 3112, right column, beginning at line 20, that

> if CPMV M RNA contained a sequence upstream of position of 512 which promoted internal initiation...synthesis of the 95 K protein would have been detected.

The studies used in Belsham and Lomonosoff used an *in vivo* system to test activity. As discussed above, it is well accepted that to assay for IRES activity *in vivo* testing must be done. Thomas et al. on the other hand used only a rabbit reticulocyte

system for testing. As further stated in Belsham and Lomonosoff the *in vivo* system used in their experiments,

> is not prone to give false positives for internal initiation...often associated with in vitro translation systems such as rabbit reticulocyte lysates. Page 312, right column, lines 34-38.

Thus, the disclosure contained in Thomas et al. that CPMV M-RNA contains an IRES is scientifically incorrect and the reported activity is, in fact, an artifact of the ODC gene in which they inserted the CMPV middle component. As such, Thomas et al. does not disclose the present invention and withdrawal of the rejection is respectfully requested.

Although an artifact claims give broadest reasonable interpretation Thomas et al does disclose an IRES. Its silent

Should the Examiner have any questions regarding the present application he is requested to please contact MaryAnne Armstrong, PhD (Reg. No. 40,069) in the Washington DC area at (703) 205-8000.

A marked-up version of claims 23 and 24 showing all changes is attached hereto.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fee

required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

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**MARKED-UP VERSION SHOWING CHANGES**

**IN THE CLAIMS**

Claims 23 and 24 have been amended as follows.

23. (Amended) The recombinant nucleic acid sequence according to claim 19, 20 or 21, wherein said IRES is a nucleic acid sequence upstream of the movement protein gene of a plant virus belonging to the group of tobamoviruses and **is** ~~exhibiting IRES-activity, i.e. being~~ capable of promoting expression of the 5'-distal genes from bicistronic and/or polycistronic mRNAs in eukaryotic cells.

24. The recombinant nucleic acid sequence according to claim 19, 20 or 21, wherein said IRES is a nucleic acid sequence upstream of the coat protein gene of a plant virus belonging to the group of tobamoviruses and **is** ~~exhibiting IRES activity, i.e. being~~ capable of promoting expression of the 5'-distal genes from bicistronic and/or polycistronic mRNA in eukaryotic cells.